



# First evidence for the use of polyamines as nucleophiles in a regioselective palladium-catalyzed allylic amination reaction



Cyril Pieri, Sébastien Combes, Jean Michel Brunel\*

Centre de Recherche en Cancérologie de Marseille (CRCM), CNRS, UMR7258, Institut Paoli Calmettes, Aix-Marseille Université, UM 105, Inserm, U1068, F-13009 Marseille, France

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## ABSTRACT

Palladium-catalyzed reaction of unsymmetrical allylic electrophiles with polyamines gives rise to regioisomeric allylic polyamines. An original catalytic procedure providing an efficient method for the regioselective synthesis of new classes of polyamino derivatives of biological interest is reported. Based on experimental considerations, a mechanistic rationale involving a thermodynamically controlled isomerization of the initially formed branched product is proposed to account for the total regioselectivity observed.

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## 1. Introduction

In the last 10 years, polyamino derivatives have attracted a considerable interest for the searchers emphasizing the fact that these compounds possess good to excellent antitumoral and antimicrobial activities for a potential use in human therapeutics.<sup>1</sup> In this context, we previously reported the ability of squalamine, a natural marine polyaminosterol compound, and of polyaminogeranic derivatives to induce a significant decrease of antibiotic resistance in Gram-negative bacterial MDR strains.<sup>2,3</sup> More recently, we patented the synthesis of polyamino polyisoprenyl derivatives and their use as original chemosensitizers to combat antibiotic resistant Gram-negative bacteria.<sup>4</sup> As it will be discussed below, the major problem for the synthesis of such derivatives consists in the regioselective outcome of the reaction involved. Thus, controlling regioselectivity has been an important goal in transition-metal-catalyzed allylic substitution<sup>5,6</sup> due to the frequent occurrence of branched allylic amines among natural products and pharmaceuticals.<sup>7</sup>

In this paper, we will report for the first time a new general procedure for the preparation of various polyamino allylic compounds involving a palladium-catalyzed reaction of unsymmetrical allylic electrophiles with polyamines. We will probe unambiguously the regioselectivity through a thermodynamically controlled isomerization of the initially formed kinetic branched product and we will propose a mechanistic rationale based on detailed experiments.

## 2. Results and discussion

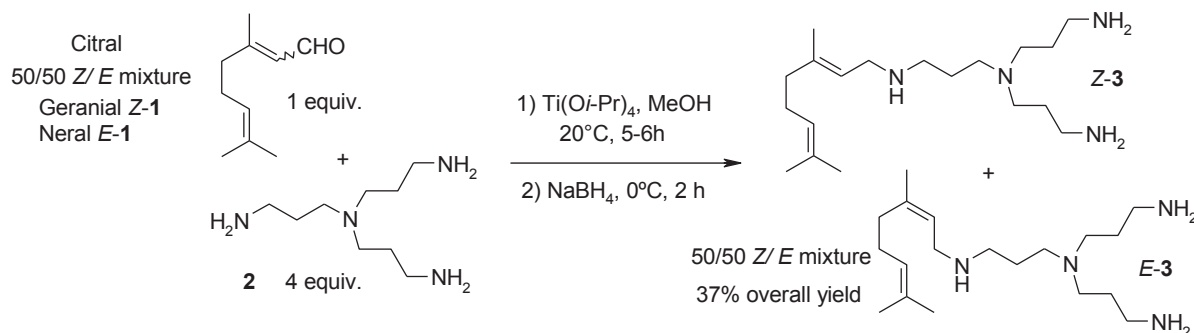
Few years ago, the preparation of polyaminoisoprenyl derivatives as a mixture of *Z/E* isomers has been reported by our group involving a titanium reductive amination reaction between a polyamine and an isoprenyl aldehyde compound.<sup>4</sup> Typically, our initial experiments were performed using citral **1** (a 50:50 mixture of neral and geranial) and tris(3-amino-propyl)amine **2** as test substrates. Under these experimental conditions, the expected compounds were obtained in moderate yield (around 37% yield) and as a mixture of the two isomers in an equal amount without the possibility to easily separate them (Scheme 1).

In this work, we have envisioned the ability to prepare selectively one of these isomers. Our first approach dealt with the use of a titanium amination reaction involving pure isomers of neral or geranial as starting materials. Nevertheless, the needed pure aldehydes not being easily available, we have developed an efficient methodology to prepare neral and geranial. This has been achieved in a selective manner from 90% pure isomer form of nerol and geraniol, respectively, by a MnO<sub>2</sub> oxidation at room temperature in toluene. In both cases, neral and geranial were obtained in 92 and 88% yields (90% pure isomer forms), respectively (Scheme 2).

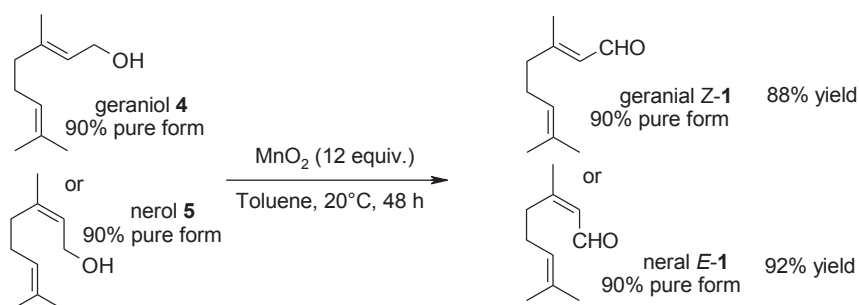
Surprisingly, a subsequent titanium amination reaction in methanol in the presence of tris(3-amino-propyl)amine led to a mixture of the *Z/E* isomers in around a 50:50 ratio in a non-optimized 35% isolated yield (Scheme 3).

Thus, whatever the experimental conditions applied (data not shown) it was impossible to obtain the expected polyamino

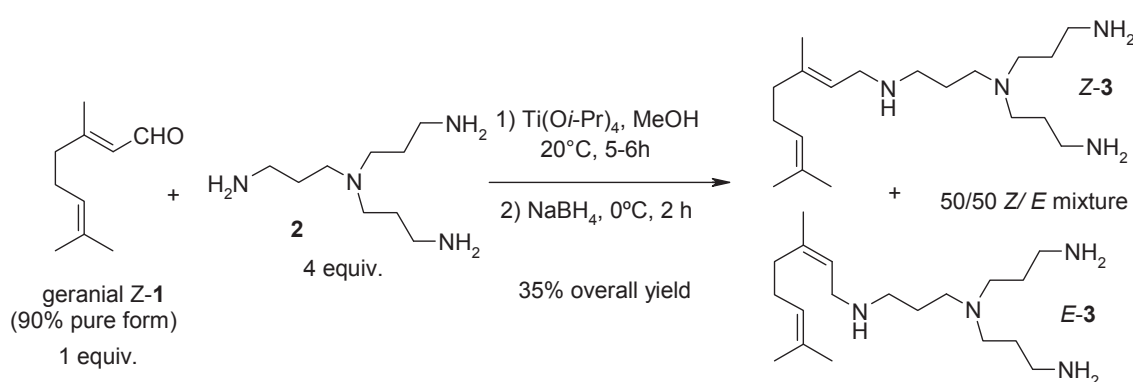
\* Corresponding author. E-mail address: [bruneljm@yahoo.fr](mailto:bruneljm@yahoo.fr) (J.M. Brunel).



**Scheme 1.** Titanium(IV) reductive amination of citral (50:50 mixture of geranial *Z*-1 and neral *E*-1) with tris(3-amino-propyl)amine **2**.



**Scheme 2.** Synthesis of pure geranial *Z*-1 and neral *E*-1 by a  $\text{MnO}_2$  oxidation of geraniol **4** and nerol **5**.



**Scheme 3.** Titanium(IV) reductive amination of geranial *Z*-1 with tris(3-amino-propyl)amine **2**.

derivatives in a pure stereoselective manner. We have been able to demonstrate that this racemization occurs by mixing the pure aldehyde and the amine in the absence of titanium isopropoxide. Indeed, after 2 days the corresponding imines were obtained as a mixture of the two isomers suggesting an isomerization process during the imine formation. The reaction mechanism of amine addition to carbonyl compounds has been widely studied at the experimental<sup>8</sup> and theoretical<sup>9</sup> levels pointing out that the isomerization occurs by inversion of the nitrogen atom.<sup>10</sup> The first step can lead to the formation of an aminoalcohol intermediate subsequently followed by a water elimination step of the aminoalcohol leading to the formation of the imine (Scheme 4).

From part these disappointing results, we have envisioned a new and original strategy involving a palladium allylic amination devoted to the synthesis of polyaminoisoprenyl derivatives. Thus, palladium has become, over the last 30 years, the most versatile transition-metal in metal-catalyzed reactions particularly those

involving carbon–nitrogen and carbon–carbon bond formation. Numerous articles reported the use of primary or secondary amines as nucleophiles but none involving a polyamine as a nucleophile in a palladium-catalyzed allylic amination reaction.

Geranyl acetate **8** was chosen as test substrate and the reaction was carried out using tris(3-amino-propyl)amine **2** as polyamine nucleophile under various experimental conditions. The formation of four different products could be monitored, depending on the applied reaction conditions (Scheme 5).

Thus, in all cases compound **3** appeared to be the major compound formed as the thermodynamic product of the reaction and has been encountered only in the *Z* isomer pure form (Table 1). Dialkylated products **9** and **10** were also isolated as well as the branched kinetic product **11** but in low to moderate yields depending on the experimental conditions applied.

Although compound **3** has been determined to be formed in 82% HPLC yield performing the reaction in EtOH (96%) (Table 1, entry 2),

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